



# PERCUTANEOUS RADIOFREQUENCY ABLATION AS A FIRST LINE TREATMENT FOR HEPATOCELLULAR CARCINOMA – PROSPECTIVE COHORT STUDY FROM A TERTIARY CARE CENTRE, KERALA, INDIA

Vishnu V Nair<sup>1</sup>, Srikanth Moorthy<sup>2</sup>, Sreekumar.K.P<sup>3</sup>, K.R.Sundaram<sup>4</sup>, Vijay Anand V<sup>5</sup>, Remya Sudevan<sup>6</sup>

<sup>1</sup>Senior Resident, Department of Radiodiagnosis, Gokulam Medical College and Research Foundation, Aalamthara - Bhoothamadakki Rd, Venjaramoodu, Kerala, India.

<sup>2</sup>Clinical Professor and Head of the Department of Radiodiagnosis, Amrita Institute of Medical Sciences & Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.

<sup>3</sup>Clinical Professor, Department of Radiodiagnosis, Amrita Institute of Medical Sciences & Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.

<sup>4</sup>Professor and Head of the Department of Biostatistics, Amrita Institute of Medical Sciences & Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.

<sup>5</sup>Specialist gastroenterologist, Aster clinic, Al Qusais, Damascus Street, Dubai, UAE.

<sup>6</sup>Consultant Clinical Epidemiologist, Departments of Health sciences research & Cardiology, Amrita Institute of Medical Sciences and Research Centre, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India.

## ABSTRACT

**Introduction:** There is scarcity of Indian data on the effectiveness of radiofrequency ablation (RFA) as the first line therapy. The aim of the study was to evaluate the recurrence rate after RFA as the first-line therapy for early-stage hepatocellular carcinoma (HCC). **Materials and Methods:** Hospital based prospective cohort study. The study period was from September 2016 to August 2018, during which 61 patients with early stage HCC without coagulopathy were included into the study after obtaining written consent. Image guided RFA was performed as a first-line treatment for early HCCs with a maximum diameter of 3 cm or solitary tumour with a diameter of <5 cm. Follow up was performed on day 1 post procedure to identify residue and for a period of 2 years after which results were analyzed for tumor recurrence, as well as recurrence-free survival time. Chi Square test was used to analyse the association of recurrence, event free survival and local tumour progression. Kaplan Meir survival analysis was used to find the event free survival. **Results:** The recurrence rate was 54.1%. The Local Tumour Progression rate was 36.36%; and the Intra hepatic distant recurrence rate was 51.51%. The overall 2-year survival was 96.73%. The event free survival for 2 years was 17.87 months (95% CI 16.0, 19.6 months). Significant predictive factors for poor recurrence free survival were age>65 years, AFP levels >200 ng/ml and multiple tumour. **Conclusion:** Percutaneous RFA can be used as first-line treatment for early stage HCC.

**KEYWORDS:** Radiofrequency Ablation, Hepatocellular Carcinoma, Predictors, Recurrence Rate, Event Free Survival.

## INTRODUCTION:

Hepatocellular carcinoma (HCC) is coming under primary liver cancer.<sup>1</sup> According to the latest GLOBOCAN 2020 report, primary liver cancer is the sixth most common cancer and third leading cause of cancer death globally.<sup>1</sup> The incidence and mortality of primary liver cancer are 2 to 3 times higher in men.<sup>1</sup> In the primary liver cancer HCC constitutes 75-85% of cases.<sup>1</sup> Most HCC cases (>80%) occur in either sub-Saharan Africa or in Eastern Asia.<sup>2</sup> Most Asian countries are in the intermediate to high incidence zone of HCC.<sup>3</sup> The age adjusted incidence rate of HCC in India for men is 0.7 to 7.5 and that for women is 0.2 to 2.2/100,000 population / year.<sup>3</sup> The male: female ratio for HCC in India is 4:1.<sup>3</sup> The age of presentation of the disease is 40 to 70 years and the age standardized mortality rate for men is 6.8/100,000 and that for women is 5.1/100,000.<sup>3</sup> The incidence of HCC in cirrhosis patients in India is 1.6% per year.<sup>3</sup>

The relative low prevalence of HCC in India compared to the prevalence around the world is due to an under-reporting of the disease as a result of which India erroneously falls in the low incidence zone.<sup>4</sup> The major risk factors for HCC are chronic hepatitis B/C infection, aflatoxin contaminated foods, chronic more alcohol intake, overweight, Type 2 diabetes mellitus and smoking.<sup>1</sup>

Globally the incidence of HCC is increasing due to the dissemination of hepatitis B and C virus infections. Patients with cirrhosis should undergo HCC surveillance once in 6 months. Surveillance of these patients allows the diagnosis of HCC at an early stage, which has multiple treatment options like resection, percutaneous ablation (RFA), Transarterial chemo embolisation (TACE), microwave ablation, liver transplantation etc. with better outcomes.<sup>1,2,3</sup>

The efficacy and clinical implications of percutaneous radiofrequency ablation (RFA) in the treatment of early-stage hepatocellular carcinoma (HCC) has been growing. At present RFA is considered as a curative modality for early-stage HCC, with outcomes comparable to those of surgery, as evidenced by many studies.<sup>2-5</sup> Clinical roles of percutaneous RFA are actually more meaningful than those of surgery as RFA could be applied to patients whose hepatic functional reserve is insufficient to endure surgery, with an advantage that it can be repeated for the same patient.

On review of literature, there seems to be a dearth of Indian data on the efficiency

of RFA as the first line therapy and the prognostic factors. Considering the reported demographic variability of HCC and its effect on the chosen modality of treatment and subsequent outcomes, the need for a study in the south Indian population to investigate the effectiveness of RFA therefore, is pertinent.

The aim of this prospective cohort study was to evaluate the role of radio frequency ablation (RFA) as a first line of treatment in patients with early stage hepatocellular carcinoma and to determine the overall survival rates and factors that help in prognostication.

## MATERIALS AND METHODS:

**Study setting:** This study was conducted in the radiology department at Amrita institute of medical sciences and research centre, Kochi, Kerala, a 1500 bedded tertiary care centre in Kerala, Southern India. During the study period, RFA procedure was performed percutaneously under image guidance on patients based on the selection criteria. This study was approved by the ethics committee of the study institution. A written informed consent from patients was obtained at the time of enrollment of the study.

**Study design:** Hospital based prospective cohort study

### Inclusion criteria:

1. Presence of a single nodular HCC <5 cm in maximum diameter;
2. Presence of three or fewer HCC nodules ≤3 cm
3. Absence of portal venous thrombosis
4. Child-Pugh class A or B
5. Prothrombin time ratio >50% (Prothrombin time with an international normalized ratio <1.7) and
6. platelet count >50,000 cells/mm<sup>3</sup> (50 cells × 10<sup>9</sup>/L)

### Exclusion criteria:

1. Presence of vascular invasion or extra hepatic metastases

## 2. Previous treatment for HCC

**Sample size:**

Based on the results available (62% recurrence and 68% survival rate) in an earlier publication (Ten year outcomes of percutaneous radiofrequency ablation as first line therapy of early hepatocellular carcinoma: Analysis of prognostic factors, Journal of hepatology, 2013, vol 58 / 89-97) and with an allowable error of 20% with 95% confidence level the minimum sample size was estimated to be 60.

**Study population:**

Out of the 161 RFA's that were performed for HCC in our hospital during the study period of 2016-2017, 61 patients who were eligible for the study were included.

**Diagnosis and Staging of HCC:**

Underlying liver disease severity was assessed by Child Pugh criteria. Investigations to determine the underlying etiology were also done. Physical examination, laboratory tests and imaging studies were performed before RFA treatment to detect any possible contraindications for RFA. The diagnosis of HCC was made using the non invasive criteria defined by the American Association for the Study of Liver Disease (AASLD) guidelines which consisted of arterial hyper enhancement with washout seen on portal or delayed-phase images.<sup>67</sup>

Out of 83 tumors, 61 tumors which were initially diagnosed and treated with imaging guided percutaneous RFA as a first-line option were analyzed in this study.

Demographic, clinical data, Child Pugh class, AFP level, radiological characteristics of the tumors (number, size, location, proximity to the vessels, proximity to the organs, presence of capsule, enhancement and washout pattern) were recorded at presentation.

After obtaining informed consent, RFA procedure was performed percutaneously under imaging guidance on an Inpatient basis. The first follow-up study was performed on the next day after the procedure to identify residue and then 1 month after the procedure. If RFA was considered to be technically effective, then a follow-up was repeated every 3 months until two years after RFA. The outcome was defined as died/survived in each case.

Patients who showed specific clinical or radiological features such as headache or abnormality in chest radiograph underwent appropriate imaging examinations for the detection of extra hepatic recurrence (ER).

**Treatment strategy after initial RFA:**

When an unablated residual tumor was observed at the immediate follow-up a repeat RFA was attempted. If percutaneous RFA was technically feasible, other therapeutic modality like (TACE) was not carried out. If the index tumor was completely covered by the ablation zone, the treatment was regarded as a technical success regardless of the sufficiency of ablative margin. If local tumor progression (LTP) or intrahepatic distant recurrence (IDR) was observed during subsequent follow-up visits, an additional treatment was immediately performed, preferably using percutaneous RFA.

**Analysis of therapeutic efficacy and survival:**

Local therapeutic efficacy in terms of technique effectiveness and LTP was assessed as per tumor basis.

IDR, extra hepatic recurrence (ER), event-free survival, were evaluated on a per-patient basis. The overall survival (OS) time was defined as the interval between the first RFA and either death or last follow-up visit.

Event-free survival was defined as the time from the first RFA to either the earliest event (i.e., LTP, IDR, ER or death) or the last follow-up date without an event.

**Definitions of terminology:**

Definitions are based on the standardization by the International Working Group on Image-Guided Tumor Ablation.<sup>8</sup>

- Technical success was defined when the tumor was treated according to the protocol and was completely replaced by RFA zones at the immediate follow-up the next day after the procedure.
- Achievement of technique effectiveness was defined when complete ablation of macroscopic tumors was evident on the 1-month follow-up exams for those patients whose HCC tumors were completely removed by the initial RFA treatment.
- LTP was diagnosed when a follow-up exam demonstrated findings of interval development/growth of the tumor along the margin of the ablation zone where the RFA had been considered to be technically effective.
- IDR was defined by a lesion with similar characteristics but not contacting the original ablation zone in the liver.

- Cancer seeding was regarded as extra hepatic recurrence

**Statistical analysis:**

Statistical analysis was performed using IBM SPSS (Statistical Package for social sciences) version 20.0 software. Categorical variables are expressed using frequency and percentage. Numerical variables are presented using mean and standard deviation. To find the association of all underlying liver disease severity related factors, tumour related factors with recurrence, local tumour progression and event free survival, Chi Square test was used. Kaplan Meir survival analysis is used to find the event free survival. The significant variables were identified and multiple logistic regression analysis was done. Mean and standard deviation was calculated for age and tumour size.

**RESULTS:****Baseline characteristics:**

A total of 61 patients were there for the final analysis. The mean age of presentation of the study participants was 64.77 (8.48) years. Out of the 61 cases, 1 (1.6%) was in the age group of 39-49 years, 15 (24.6%) were in the age group of 50-59 years, 25 (40.9%) of the patients were in the age group of 60-69 years, 20 (32.8%) were in the age group of 70-79 years. The baseline characteristics of the study population are represented as Table 1.

**Table 1: Baseline characteristics of the study population**

Study variables	Frequency	Percentage (%)
Demographics		
Age (yrs)	n=61	
39-49	1	1.6
50-59	15	24.63
60-69	25	40.98
70-79	20	32.79
Gender		
Male	58	95
Female	3	5
Liver disease severity		
Child Pugh Criteria		
A	40	66
B	21	34
AFP Level (ng/ml)		
<20	17	28
20-200	27	44
>200	17	28
Etiology		
HCV	21	34.4
HBV	24	39.3
HCV+HBV	4	6.6
Hepatitis non-B, non-C virus	5	8.2
Cryptogenic	2	3.3
Current alcohol consumption	4	6.6
No liver disease	1	1.6
Tumor related factors		
Tumor number		
1	43	70
2	14	23
3	4	7
BCLC criteria		
0	20	33
A	41	67
Tumor size of solitary tumor (n=43)		
0.5-1 cms	5	12
1.1 – 2 cms	15	35
2.1-3 cms	11	25
3.1-4 cms	7	16
4.1-4.9 cms	5	12
Tumor size of multiple tumor (n=40)		
0.5-1 cms	9	22
1.1– 2 cms	20	50
2.1-3 cms	11	28

Location in segment of liver (n=61)		
Seg 1	2	3.20
Seg 2	3	4.91
Seg 3	2	3.30
Seg 4A	1	1.60
Seg 4B	1	1.60
Seg 5	7	11.50
Seg 6	21	34.40
Seg 7	13	21.30
Seg 8	10	16.40
Seg 7+8	1	1.61
Proximity to vessels (n=61)		
Portal Vein	3	4.92
IVC/HV junction	2	3.27
Hepatic Vein	1	1.64
Not close	55	90.17
Proximity to organs (n=61)		
Sub capsular	5	8.19
Diaphragm	3	4.92
Gall bladder	2	3.27
Stomach	2	3.27
Colon	1	1.63
Pericardium	1	1.63
Not close	47	77.00
Presence of capsule (n=61)		
Yes	42	69
No	19	31
Enhancement pattern (n=61)		
Typical	58	95
Atypical	3	5
Tumor washout (n=61)		
Typical	61	100

\*AFP-Alpha- fetoprotein

\*\*HBV-Hepatitis B virus

\*\*\*HCV-Hepatitis C virus

#BCLC criteria- Barcelona clinic liver cancer staging criteria

##IVC/HV- Inferior vena cava/ Hepatic vein

Recurrence and treatment:

Among the 61 patients 33 (54.1%) had recurrence, 2 (3.27%) died and 3 (4.91%) had residue within the study period. Out of the 33 (54.1%) patients who developed recurrence on follow up, 21 (34.42%) patients had second recurrence after treatment and 3 (4.9%) patients developed a third recurrence within the two year period.

Out of the 33(54.1%) patients who developed recurrence 17 (51.52%) patients had intra-hepatic distant recurrence (IDR), 12 (36.36%) had local tumour progression (LTP), 3 (9.09%) patients had both LTP and IDR and 1(3.03%) patient had extra hepatic recurrence (ER).

Among the 33 patients who had recurrence 32 tumours were present in the liver and 1 was present at a extra hepatic site. Therefore 32 tumours had hepatic recurrence. Most of the local tumour progression occurred in segment 6 and 7 with IDR more in segments 6 followed by segment 5. LTP with IDR occurred in segments 5 and 8.

Among the 33 patients who had first recurrence, 22(67%) were treated with repeat RFA, 8 (24%) were treated with TACE, 2 (6%) were treated with RFA with TACE and 1 (3%) was treated with chemotherapy. The types of recurrence and treatment of the recurrence are shown in Table 2.

**Table 2: Types and treatment of recurrence of HCC after RFA**

Types of recurrence	Frequency (%)		
	1 <sup>st</sup> recurrence (n=33)	2 <sup>nd</sup> recurrence (n=21)	3 <sup>rd</sup> recurrence (n=3)
IDR	17 (51.52)	14 (66.67)	2 (66.66)
LTP	12 (36.36)	5 (23.81)	

LTP+IDR	3 (9.09)	1 (4.76)	1(33.34)
ER	1 (3.03)	1 (4.76)	
Treatment for recurrence			
RFA	22 (67)	5 (23.82)	1(33.33)
TACE	8 (24)	11 (52.38)	
RFA+TACE	2 (6)	2 (9.52)	1(33.33)
Chemotherapy	1 (3)	1 (4.76)	
Palliation		2 (9.52)	
Transplant			1(33.33)

\*IDR- Intrahepatic distant recurrence

\*\*LTP- Local tumor progression

\*\*\*ER- Extra hepatic recurrence

#RFA-Radiofrequency ablation

##TACE- Transarterial chemo embolisation

**Overall survival (OS):**

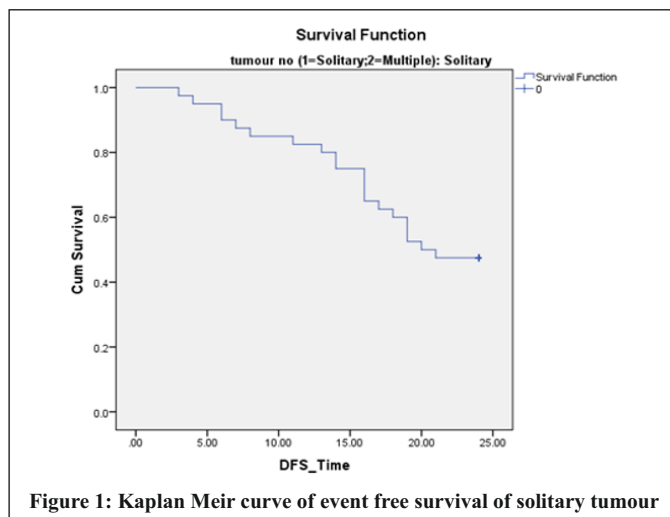
In our study the overall survival at 2 years was 96.73%.

Event free survival:

The overall event free survival was 17.87 months with 95% CI 16.0, 19.6 months.

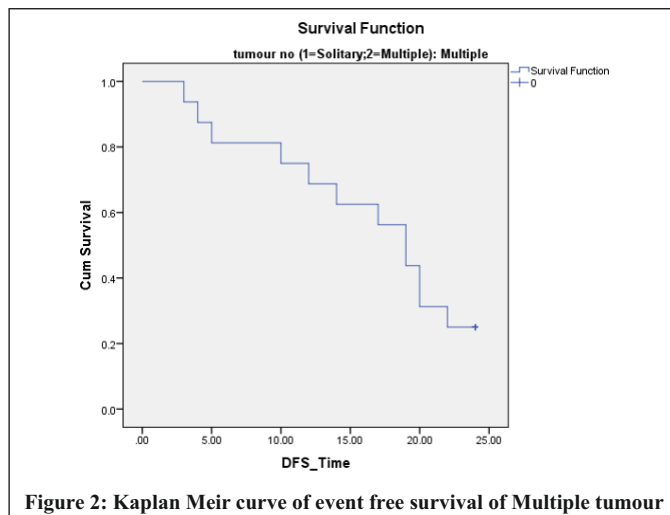
The mean estimate of event-free survival for solitary tumours (n=43) was 18.47 months with 95% CI 16.4, 20.5 months. The details are represented in Fig 1.

The mean estimate of event-free survival for Multiple tumours (n=18) was 16.31 months with 95% CI 12.7, 19.85 months. The details are represented in Fig 2.



Cum survival- Cumulative survival

DFS- Disease free survival



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**Prognostic factors for recurrence (LTP/IDR/ER):**

Out of the 61 patients, 2 patients died before recurrence and 3 patients had residual tumour, therefore 56 patients were followed up for recurrence. Among them, 33 developed recurrences in the 2 year follow up. When the subgroup comparison was done to find the association of different prognostic factors with recurrence, we couldn't find any association with the selected variables and recurrence. The details are represented in Table 3.

**Table 3: Predictors affecting recurrence of HCC after RFA**

Variables	Recurrence		P value
	Yes	No	
Age (SD)	65.45 (7.51)	62.61 (9.45)	0.21
Gender (n, %)			
Male (53, 94.6%)	31 (58.5%)	22 (41.5%)	1.00
Female (3, 0.05%)	2 (66.7%)	1 (33.3%)	
Child Pugh criteria (n, %)			
A 37(66.1%)	21 (56.8%)	16 (43.2%)	0.65
B 19(33.9%)	12 (63.2%)	7 (36.8%)	
AFP level in ng/ml (n, %)			
<200 41(73.2%)	21 (51.2%)	20 (48.8%)	0.10
>200 15(26.8%)	12 (80%)	3 (20%)	
Tumor number (n, %)			
<2 40(71.4%)	20 (50%)	20 (50%)	0.06
>2 16(28.6%)	13 (81.3%)	3 (18.8%)	
Tumor size in cm (n, %)			
<3 (41, 73.2%)	21 (51.2%)	20 (48.8%)	0.10
>3 (15, 26.8%)	12 (80%)	3 (20%)	
Proximity to vessels (n, %)			
Close (50, 89.3%)	29 (58%)	21(42%)	1.00
Not close (6, 0.11%)	4(66.7%)	2 (33.3%)	
Proximity to organs (n, %)			
Close (42, 75%)	27 (64.3%)	15 (35.7%)	0.16
Not close (14, 25%)	6 (42.9%)	8 (57.1%)	
Presence of capsule (n, %)			
Present (40, 71.4%)	21 (52.5%)	19 (47.5%)	0.21
Absent (16, 28.6%)	12 (75%)	4 (25%)	
Pattern of enhancement (n, %)			
Typical (53, 94.6%)	32 (60.4%)	21 (39.6%)	0.75
Atypical (3, 0.05%)	1 (33.3%)	2 (66.7%)	

\*AFP-Alpha- fetoprotein

**Factors affecting the event free survival:**

The event free survival for patients in the age group of <65 years was <12 months for 3 (11.1%) and > 12 months for 24 (88.9%). While the same for >65 years was < 12 months for 11 (32.4%) and 23 (67.6%). The difference in survival among the two age groups was statistically significant with a p value of 0.05. Hence age was a significant predictor of Event free survival. Patients with age <65 years had more than 12 months of event free survival. Similarly AFP level and tumor number were also significant predictors of event free survival. The details are shown in Table 4.

**Table 4: Factors affecting the event free survival**

Factors	Event free survival		P value
	<12 months	>12 months	
Age in years (n, %)			
<65 (27, 44.3%)	3 (11.1%)	24 (88.9%)	0.05
>65 (34, 55.7%)	11 (32.4%)	23 (67.6%)	
Child Pugh criteria (n, %)			
A (40, 65.6%)	8 (20%)	32(80%)	0.45
B (21, 34.4%)	6 (28.6%)	15 (71.4%)	
AFP level in ng/ml (n, %)			
<200 (44, 72.1%)	7 (15.9%)	37 (84.1%)	0.04
>200 (17, 27.9%)	7 (41.2%)	10 (58.8%)	
Tumor number (n, %)			
Solitary (43, 70.5%)	6 (14%)	37 (86%)	0.01
Multiple (18, 29.5%)	8(44.4%)	10 (55.6%)	
Mean Tumor size with SD in cm (n, %)			
2.28 (1.09) 61 (100%)	2.34 (1.06) 14 (22.9%)	2.20 (1.14) 47 (77.1%)	0.68
Proximity to vessels (n, %)			
Close (55, 90.2%)	11 (20%)	44 (80%)	0.25
Not close (6, 0.09%)	3 (50%)	3 (50%)	
Proximity to organs (n, %)			
Close (47, 77.0%)	12 (25.5%)	35 (74.5%)	0.61
Not close (14, 22.9%)	2 (14.3%)	12 (85.7%)	
Presence of capsule (n, %)			
Present (42, 68.9%)	7 (16.7%)	35 (83.3%)	0.08
Absent (19, 31.1%)	7 (36.8%)	12 (63.2%)	

\*AFP-Alpha- fetoprotein

\*\*SD-Standard deviation

**DISCUSSION:**

In early HCC, RFA has been proven to have comparable outcomes to hepatic resection in studies done worldwide (Gao J et al, Chen et al).<sup>8,9</sup> This is of special significance in those patients in whom hepatic resection cannot be performed due to various reasons. The main drawback of RFA cited in most studies is the rate of local tumour progression which can be circumvented by better patient selection criteria and by understanding the various factors that would lower the recurrence rates.

A total of 61 patients who fulfilled the criteria for percutaneous imaging guided RFA were included in our study and were followed up immediately (next day), at 1 month and at 3 months interval upto 2 years. Various factors, which may be broadly classified as factors relating to the underlying liver disease and tumour related factors were studied and analysed.

The demographic pattern of HCC in our study was comparable to studies from different parts of the world with age of presentation ranging from 39 years to 79 years with a mean age of presentation of 64.77(8.48) years which was similar to that found in studies done by Lee et al in which the mean age was 63.8 (9.8) years with range (28- 86 years) and 76 years (36-88 years -Gao J et al ).<sup>10,8</sup> There was a male predominance much higher than that seen in other studies which could probably be because of the higher prevalence of alcoholism amongst male patients in our part of the country which might have had an additive effect to other etiologies.

Complete tumour ablation was achieved in 95 % of the patients in our study which is comparable to studies done by Gao et al (97.8% ), Kim et al (94.8%), Shiina et al report a much higher rate at 99.4% of complete tumour ablation.<sup>8,11,12</sup>



The overall recurrence rate in our study was 59% within 2 years of follow up. A few patients, about 5%, had upto 3 recurrences. Various studies have reported recurrences ranging from 62- 69%.<sup>11,13</sup>

Of the different variables that were analysed for correlation with recurrence we did not find any significant correlation in any of the variables. However, in the review of literature tumour size  $\leq 3$  cm was found to predict greater RFA efficacy with lower recurrence in many studies and showed that the success of radiofrequency ablation of the total viable tumor tissue was highly dependent on tumor size and location.<sup>12,14</sup> Best results were recorded for tumors measuring  $< 3$  cm; furthermore, presence of large ( $> 3$  cm in diameter) abutting vessels highly limited the efficacy of RFA (heat sink effect: cooling of tumor tissue by means of vascular perfusion). Hori et al reported that recurrence is low in HCC  $< 2.3$  cm and increased if the tumor is  $> 2.5$  cm in its maximum diameter.<sup>15</sup>

Study by Komorizono et al also showed the risk factors for overall recurrence to be large tumor size, an increase in serum AFP level and the presence of hepatitis.<sup>16</sup>

Harrison et al showed that the significant risk factors for overall recurrence were a large tumor size, an increase in serum AFP level and the presence of hepatitis.<sup>17</sup>

In our study, the follow up ranged from 3 months to 21 months. The mean estimate of event-free survival was 17.87 months with 95% CI 16.0, 19.6 months. The study by Lee et al showed the mean and median recurrence-free survival were 34.2 months (95% CI: 29.8, 38.5) and 23.0 months (95% CI: 17.5, 28.5).<sup>18</sup>

Age was found to be a significant predictor of event free survival.

In our study patients who were  $\leq 65$  years had longer event free survival. Also in our study, patients with an AFP level of  $\leq 200$  ng/ml prior to RFA had a longer event free survival than patients with a higher AFP. Solitary tumours have longer event free survival in our study. On logistic regression analysis age  $\leq 65$  years was found to be a significant factor to predict longer event free survival.

In the review of literature the study by Lee et al showed a similar result where Child-Pugh class, serum AFP level were significantly associated with recurrence-free survival.<sup>18</sup> This may be related to differences in tumour biology. However a larger sample size and longer follow up may be required to confirm the observation.

The rate of local tumour progression in our study was 36.36 % which is similar to the rate reported by Harrison et al (39.1%) in their 3-year follow-up study.<sup>19</sup> Another study had a LTP incidence of 11.8% for primary uninodular HCC and 50% for primary multinodular HCC.<sup>15</sup>

Komorizono et al who studied LTP after a single application of RF energy for relatively small HCC, reported that the significant risk factors for LTP were tumor size over 2 cm in the greatest dimension and a sub capsular location.<sup>16</sup> Another study also showed an insufficient safety margin, a multinodular tumor at the time of ablation, tumors located at segments 8 and 5, and patient's age  $> 65$  years were risk factors for LTP.<sup>15</sup> But in our study none of these risk factors were found to be statistically significant for the prediction of LTP. This could again be a pitfall of the small sample size and short duration of follow up.

Lee et al also has reported tumor size as the only significant predictor for developing LTP in their study.<sup>18</sup> In their study, Lee et al had also estimated that patients with LTP required approximately three more interventional procedures than those patients who did not have LTP to obtain a similar overall survival outcome. Hence a sufficient safety margin should be attained, especially in larger tumors where there is more chance for LTP.

Intra hepatic Distant Recurrence (IDR) was seen in 51.51% of our patients which is comparable to the other studies in which the IDR was 53.2% and 52.5%.<sup>11,13</sup> Patients with multiple tumours had a high incidence of IDR within 12 months which has affected the event free survival, though the median size of the target lesion in these patients was smaller than in patients with solitary tumour.

In our study the overall survival at 2 years was 96.73%. These are also comparable to other studies in literature.<sup>8,11,12,16,19,20</sup> The factors in the study by Kang et al for poor overall survival were old age, Child-Pugh class B, absence of antiviral therapy during the follow-up period, or occurrence of extra hepatic recurrence. Aggressive antiviral therapy after radiofrequency ablation appears to prolong survival of the patients if the underlying liver disease is related to hepatitis viral infection.<sup>21</sup> The findings from the study by Lee et al showed significant predictive factors for poor overall survival were Child-Pugh class B, serum AFP level and the presence of portosystemic collaterals.<sup>10</sup>

The BCLC criteria serves to provide a more holistic assessment of the patient by including liver function related, tumour related and performance related factors. Only patients with BCLC stage 0 and A were included in our study. 67% of our patients were BCLC stage A. Though theoretically, a tumor that is contiguous to a large vessel has more chance of allowing some tumor cells to survive local thermal therapy because of significant tissue cooling of circulating blood only few

studies have found a significant correlation. Lee et al showed treatment failures developed in a tumour with a close proximity to the right hepatic vein.<sup>10</sup> Our study did not show any significant risk in treatment failure or recurrence due to tumour proximity to organs or vessels.

#### LIMITATIONS OF THE STUDY:

The limitations of our study were our small sample size and a limited follow up period. The diagnosis of HCC was based on AASLD criterion which does not require biopsy. In the absence of histopathological proof, the role of tumour biology cannot be factored. Procedure related factors that could have influenced the efficacy of treatment response of RFA were not analysed. Moreover the ablations were performed by multiple operators and difference in the individual skills could also have played a role. As one of the major limitations of RFA is larger tumour size, combining therapies like Microwave ablation /trans arterial therapies or other combined approaches may help to achieve better outcomes for HCC lesions measuring up to more than 3 cm. Genetic heterogeneity is an important unknown variable impacting tumour biology and subsequently recurrence rate.

#### CONCLUSIONS:

The overall survival at 2 years was 96.73%. The overall event free survival was 17.87 months with 95% CI 16.0, 19.6 months. The Local Tumour Progression rate was 36.36% and the Intra hepatic distant recurrence rate was 51.52%. Patients with age  $\leq 65$  years had a longer event free survival. All these findings show that Percutaneous RFA can be used as the first-line treatment for early stage HCC.

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